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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,140	02/09/2007	Arturas Petronis	034263.002 (08899871US1)	1527

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
11/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/598,140	PETRONIS ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER M. BABIC	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,20 and 21* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/27/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claim(s) 1, 2, 4-9, 20, 21 are pending. Claim(s) 1, 2, 4-9, and 21 are under examination. The following Office Action is in response to Applicant's communication dated August 13, 2009.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on July 27, 2009 was filed after the mailing date of the NON-FINAL Office Action on February 13, 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

The objection to the specification has been withdrawn in view of Applicant's amendments.

Claim Objections - Withdrawn

Applicant's claim amendments are sufficient to overcome the objection of claim(s) 1-19, 21, and 22 presented in the Office Action dated February 13, 2009.

Claim Rejections - 35 USC § 112 - Indefiniteness - Withdrawn

Applicant's claim amendments are sufficient to overcome the rejection of claim(s) 2-4, 7-9, 17-19, and 21 presented in the Office Action dated February 13, 2009.

Claim Rejections - 35 USC § 102 - Withdrawn

Claims 10-19 were cancelled rendering the previous rejections moot.

Claim Rejections - 35 USC § 103 - Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1 and 4-9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S) or

Huang (U.S. 6,605,432 B1) in view of Chotai et al. (J Med Genet. 1998 Jun;35(6):472-5).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the successive digestion of a nucleic sample with a methylation sensitive restriction enzyme followed by a methylation specific restriction enzyme.

With regard to claims 1, 5-9, and 22, Chotai provides a supportive disclosure that teaches the use of a methylation sensitive restriction enzyme (Not1) in conjunction with a methylation specific restriction enzyme (McrBC) to differentiate methylation status of target nucleic acids (abstract; fig. 1; pg. 473, SNRPN status, for example). It is clear from the teachings of the reference that the use of methylation sensitive restriction enzymes allow for the isolation or production of nucleic acid target sequences that contain collection of specific methylation sites, i.e. methylated CpG islands or fragments in between unmethylated CpG sites, as methylated CpG sites are not digested due to the sensitivity of the restriction enzyme (e.g. Not1).

Returning to the teachings Yan and Huang, the methods clearly require intact fragments of DNA based on the methylation of CpG sites for further analysis of methylation, thus a skilled artisan would have been motivated to utilize restriction enzymes that produce such fragments.

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize a methylation

sensitive restriction enzyme within the first digestion steps of the methods within Yan and Huang since the prior art demonstrates such enzymes as useful for producing intact fragments of DNA based on the methylation of CpG sites. It would have been further obvious to include a methylation insensitive enzyme to produce fragments between such methylated sites for further analysis.

With regard to claim 4, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize McrBC within the second digestion steps of the methods within Yan and Huang since the prior art demonstrates such an enzymes as useful for digesting methylation specific nucleotide sites.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

In response to Applicant's arguments against the references individually (remarks pg. 11-14, 16), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's arguments asserting that the proposed modification would change the principle operation of the prior art as well as leave the prior art unsatisfactory for its intended purpose (pg. 14-15), the examiner respectfully disagrees. First the examiner understands that using a methylation sensitive enzyme in the first

restriction digest of the Yan or Huang method would create different products for subsequent analyzing; however, that the examiner believes that the production of those products would have been obvious to person of ordinary skill in the art. The prior art, .i.e. Chotai, clearly recognizes that the analyzing of unmethylated DNA was of interest at the time of invention. An artisan wanting to analyze such unmethylated DNA by the high-throughput methods of Yan or Huang would have understood that the enzymes used within the sequential digestions would have needed to be changed in order to accommodate the target methylation patterns. In other words, the examiner is asserting that it would have been obvious to analyze unmethylated DNA within the methods of Yan or Wang through modification of the restriction enzymes. The examiner is not changing the principle operation or intended function of the Yan or Huang method by the proposed modification, i.e. analyzing the presence of methylation or lack thereof. Moreover, an artisan of ordinary skill in the art would have expected the proposed modifications to operate in a predictable manner.

Thus, the rejection is maintained.

2. Claim 2 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S) or Huang (U.S. 6,605,432 B1) in view of Chotai et al. (J Med Genet. 1998 Jun;35(6):472-5) as applied to claim 1 above, and in further view of Dean et al. (U.S. 6,617,137 B1).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the amplification of target nucleic acid sequences prior to start of the methylation analysis methods.

Dean provides a supportive disclosure that teaches simplified methods of whole genome amplification for further biochemical analysis (abstract; col. 2-7, summary; col. 37, use of Phi29 DNA polymerase, for example). The reference further highlights that the availability of an adequate quantity and quality of genomic DNA, which is frequently limiting in samples, is fundamental to genetic analysis (col. 1, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize the Phi29 based genome amplification methods of Dean to amplify the disease and non-disease genomic DNA used within the methods of Yan and Huang, prior to the start of such methods, since the prior art demonstrates such a methods as useful for providing an adequate quantity and quality for genomic analysis.

3. Claim 21 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S) or Huang (U.S. 6,605,432 B1) in view of Dean et al. (U.S. 6,617,137 B1).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the

amplification of target nucleic acid sequences prior to start of the methylation analysis methods.

Dean provides a supportive disclosure that teaches simplified methods of whole genome amplification for further biochemical analysis (abstract; col. 2-7, summary; col. 37, use of Phi29 DNA polymerase, for example). The reference further highlights that the availability of an adequate quantity and quality of genomic DNA, which is frequently limiting in samples, is fundamental to genetic analysis (col. 1, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize the Phi29 based genome amplification methods of Dean to amplify the disease and non-disease genomic DNA used within the methods of Yan and Huang, prior to the start of such methods, since the prior art demonstrates such a methods as useful for providing an adequate quantity and quality for genomic analysis.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 814-880-9945. The examiner can normally be reached on Monday-Friday 10:00AM to 6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher M. Babic/
Primary Examiner
Art Unit 1637
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